and wherein

R^1 and R^3 may together be an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring between the two nitrogen atoms, and

L is a leaving group.

REMARKS

Opioid drugs, such as morphine, are among the most powerful and widely used analgesics known. These drugs, however, are not without untoward side effects, most notably of which are the sedative and addictive effects of these drugs on the central nervous system (CNS). The present invention provides new opioid drugs that, while retaining activity in the peripheral nervous system, do not substantially affect the CNS, due to the fact that these drugs are less accessible to the CNS. Central to this advantage of these new drugs is the linkage of a charged group, via a spacer, to the nitrogen atom of the basic opioid structure. The charged group, which, by increasing the hydrophilicity of the drug, reduces passage of the drug across the blood-brain barrier into the CNS, has no adverse effects on drug efficiency.

Summary of the Office Action

Claims 1-3, 5, 7-12, 14, 16, 18-25, 28, 29, and 31-33 are pending in this application. The Examiner has objected to claim 32 under 37 C.F.R. 1.75 for being a duplicate of claim 24. Claims 1-3, 5, 7, 8, 18, 23-25, 32, and 33 stand rejected under 35 U.S.C. §112, first paragraph. Claims 1-3, 5, 7-12, 16, 18-25, 28, 29, and 31-33 stand rejected under 35 U.S.C. §112, second paragraph. Claims 7 and 31 stand rejected under 35 U.S.C. §102(b). Claims 7 and 31 stand rejected under 35 U.S.C. §103(a). Applicants address these rejections with the following amendments and remarks. First, Applicants note that claim 32 has been cancelled

to meet the Examiner's objection. Second, Applicants note that claim 14 is currently pending in this application, but is not listed on Office Action Summary.

Rejection under 35 U.S.C. §112, paragraph 1

Claims 1-3, 5, and 18 were rejected under §112, first paragraph, for inadequate written description.

Applicants have met this rejection by amending the claims to remove the language 'YN is an opioid.'

Claims 1, 7, 8, 18, 23-25, 32, and 33 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. As a basis for the enablement rejection, the Office Action at paragraph 13 recites:

> For the compounds of formula I wherein the spacer is not described in the specification but embraced by the generic claims, and the compounds of formula II wherein R1 and R3 together form a ring not specifically described in the specification, starting materials and the process for preparation of the inventive compounds is not seen but are required. Sources are particularly pertinent especially when the structures of these spacers or rings are not described. Absent sources, the public is offered mere language, rather than enablement.

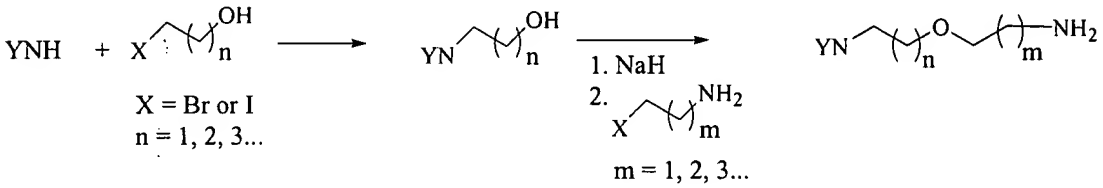
Applicants overcome this rejection with the following arguments.

Applicants' Specification Enables
The Present Claims

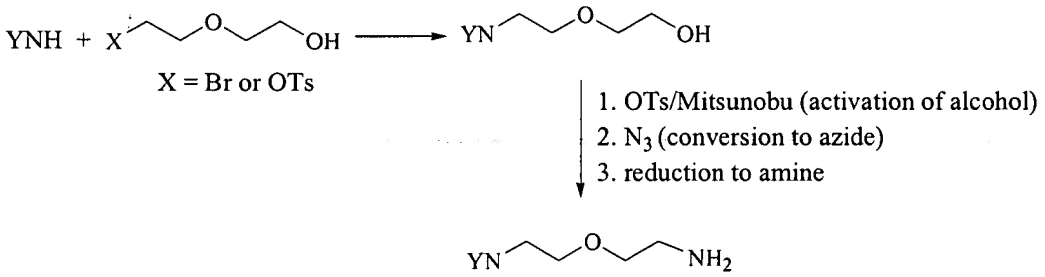
The rejection is first based on the assertion that the specification fails to enable spacers beyond those described by claims 2 and 3. Applicants respectfully disagree.

Applicants note that claim 1 has been amended to include the limitation that the spacer group has 1 to 6 atoms. It is very common to synthesize compounds with a variety of spacer groups between two functional ends of a compound. The preparation of compounds that differ only in the spacer linking YN to an amidine or guanidine group can be achieved using known chemical techniques. For

example, a compound in which the spacer is an ether can be prepared via the precursor YN-X-NH_2 in which X is an ether-containing alkylene. Reaction schemes 1 and 2 exemplify how standard chemical techniques are employed to synthesize such compounds.



reaction sheme 1



reaction scheme 2

As a second basis for the enablement rejection, the Examiner asserts that the specification fails to enable heterocyclic rings beyond those specifically described in the specification. Applicants respectfully disagree.

Applicants note that the amended claims limit the ring systems resulting from the combination of R^1 and R^3 to those in which R^1 and R^3 combined are an alkylene or alkenylene of from 2 to 4 carbon atoms. Accordingly, the present claims cover ring systems of 5, 6, and 7-membered rings. Such ring systems can be prepared via the precursor YN-spacer-NH_2 using, for example, the methods disclosed in Schlama et al., *J. Org. Chem.*, 62:4200 (1997), a copy of which is provided herewith as Exhibit A.

In view of the above evidence, it is clear that the linking of YN to an

amidine or guanidine group via any spacer and the synthesis of 5, 6, and 7-membered ring systems require only methods which are familiar to one skilled in the art of medicinal chemistry. The specification is not required to teach methods that are routine in the art. Furthermore, Applicants have provided numerous working examples of how to make compounds of the invention. With these teachings and the application of routine synthetic methodology, the claimed genus of compositions is fully enabled by the specification in a manner which allows one skilled in the art to make and use the invention.

In view of the arguments above, Applicants request withdrawal of the enablement rejections.

Rejection under 35 U.S.C. §112, paragraph 2

Claims 1-3, 5, 7-12, 16, 18-25, 28, 29, and 31-33 were rejected under §112, second paragraph.

Claim 1 stands rejected for indefiniteness based on the term 'activity in the central nervous system,' the term 'Y-N is an opioid,' the term 'spacer,' and for lacking a comma. Applicants have addressed this rejection by amending claim 1 to remove or clarify this language.

Claim 18 stands rejected for indefiniteness with respect to what method is claimed. Applicants have addressed this rejection by cancelling claim 18.

Claims 19-22 stand rejected for indefiniteness in how the claimed process results in a compound of formula II. Applicants have addressed this rejection by amending claims 19-22 to clarify what product is formed.

Claim 20 stands rejected for indefiniteness for failing to recite the step of making a compound wherein Z is an oxygen atom. Applicants have addressed this rejection by amending claim 20 to remove an oxygen atom from the definition of Z.

Claim 21 stands rejected for indefiniteness for failing to recite the step of making a compound wherein Z is an oxygen atom. Applicants have addressed this rejection by amending claim 21 to remove an oxygen atom from the definition of Z.

Claim 22 stands rejected for indefiniteness for reciting a chemical reaction as an example, but otherwise unconnected to the claim. Applicants have addressed this rejection by amending claim 22 to remove the chemical reaction.

Claim 16 stands rejected for lack of antecedent basis in claim 1, from which claim 16 depends, for compounds having no linker. Applicants have addressed this rejection by amending claim 1 to include compounds having no linker.

Claims 32 and 33 stand rejected for failing to recite the subject to whom the compound is administered. Applicants have addressed this rejection by cancelling claim 32 and amending claim 33 to recite the subject to whom the compound is administered.

Claim 33 stands rejected for failing to recite 'composition' after 'pharmaceutical.' Applicants have addressed this rejection by amending claim 33 to insert the word 'composition' after 'pharmaceutical.'

Claim 7, and subsequent dependent claims, stand rejected for indefiniteness of the term 'ring.' Applicants have addressed this rejection by amending claim 7, and claims dependent thereon, to include the limitation that R^1 and R^3 may together be an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring between the two nitrogen atoms.

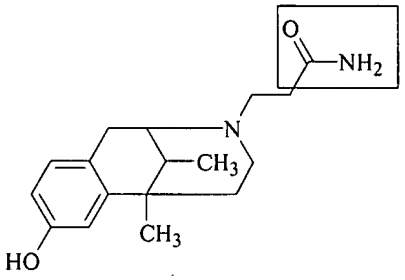
In view of these amendments, Applicants request withdrawal of the indefiniteness rejections.

Rejection under 35 U.S.C. §102(b)

Claims 7 and 31 were rejected under §102(b) as being anticipated by Maeda et al. (Pharmacobio-Dyn. 4(3):167-174, 1981). Furthermore, claims 7 and 31 were rejected under 35 U.S.C. §102(b) as being anticipated by Atsumi et al. (U.S. Patent

No. 3,950,346). Specifically, the Examiner cites the compound with RN 77943-85-2 of Maeda and the compound in example 3 of Atsumi. Applicants address both of these rejections, together, with the following arguments.

Maeda discloses the compound with RN 77943-85-2, which has the same structure (without regard to stereochemistry) as Atsumi's compound of example 3. The structure of this compound is provided below.



RN 77943-85-2

Claims 7 and 31 are not anticipated by the compositions of Maeda and Atsumi. Claim 1, from which claim 7 depends, is limited to amidine and guanidine derivatives. Claim 31 is directed to a pharmaceutical comprising a compound of claim 7 and, therefore, is also limited to amidine and guanidine derivatives. The prior art compounds cited by the Examiner are, in contrast, amide derivatives (the relevant portion of the structure is marked by a box). Thus, Maeda and Atsumi do not anticipate claims 7 or 31 because the definition of Z in formula II of claim 7 cannont include an oxygen atom.

In view of these arguments, Applicants request withdrawal of these §102(b) rejections.

Rejection under 35 U.S.C. §103(a)

Claims 7 and 31 were rejected under §103(a) for obviousness over Atsumi et al. (U.S. Patent No. 3,950,346), example 3. The Examiner states that one would be motivated to replace Atsumi's methyl with the alternative hydrogen to arrive at the instant invention. Applicants disagree.

Applicants discovered that an improved drug could be produced by linking a charged group, via a spacer, to the nitrogen atom of the basic opioid structure. The charged group increases the hydrophilicity of the drug and reduces passage of the drug across the blood-brain barrier into the CNS. Claims 7 and 31 cover such compositions in which the charged group is an amidine or guanidine group.

Furthermore, even if the modification of Atsumi proposed by the Examiner, replacement of a methyl group with a hydrogen atom were carried out, that would not result in a compound within any of the instant claims. That modification only changes the opiate portion of the structure, not the charge of the group linked to the opiate. Atsumi's opioids are linked to a neutral amide group, while the compositions of claims 7 and 31 are limited to charged amidine and guanidine groups. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness, because the compositions that result from the contributions of the cited reference would not contain every structural feature required by claims 7 or 31.

In view of the above, Applicants request that the obviousness rejection be withdrawn.

Support for the Amendments to the Claims

Claims 1 and 7 have been amended to include the compounds without a spacer separating YN from the amidine or guanidine group. Support for compounds without a spacer can be found in the specification at pages 6 and 7, which recite specific compounds without a spacer, e.g., KRS-2-19, KRS-3-23-4, KRS-3-30-2, KRS-3-7. Furthermore, claims 1 and 7 have been amended to include the language "YN is an organic residue obtained by the removal of a predetermined organic group, Q, from an opioid of the formula YN-Q." Support for this language is found in the specification at page 4, lines 14-22. Claims 1, 7, and 8 have been amended to include the language "R^1 and R^3 together form an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring including

two nitrogen atoms." Support for these ring structures is found in the specification at page 5, lines 14-25. Claim 19 has been amended to recite the amine starting materials having an alkylene spacer or no spacer. Support for these starting material can be found in the specification at page 11, lines 23-30, page 21, lines 1-11, and page 27, lines 18-30. Claims 20, 21, and 22 have been amended to recite cyano starting materials having an alkylene spacer or no spacer. New claim 34 also recites cyano starting materials having an alkylene spacer or no spacer. Support for these starting materials can be found in the specification at page 12, lines 14, to page 13, line 25, page 15, lines 9-21, page 20, lines 24-36, and page 21, lines 14-24. These amendments do not introduce any new subject matter.

Conclusion

Applicants submit that the claims are now in condition for allowance and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for three months, to and including February13, 2003.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: Feb. 13, 2003

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Reg. No. 30,162

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101 Federal Street
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Facsimile: 617-428-7045

"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

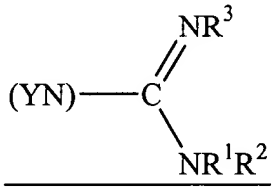
In the claims:

1. (Three Times Amended) A compound having the formula:

(~~Y-N~~ YN)-(spacer)-(amidine or guanidine group)

(~~I~~)

or

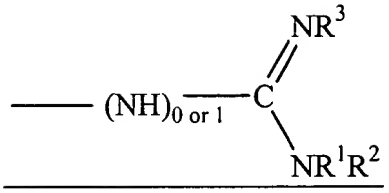


wherein

~~Y-N~~ (YN) is an ~~opioid~~ organic residue obtained by the removal of a predetermined organic group, Q, from an opioid of the formula YN-Q, said opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine; ~~, and N in Y-N is a nitrogen atom of said opioid, to which is linked a spacer, which links said compound to an amidine or guanidine group~~

(spacer) is a group linking YN to an amidine or guanidine group, wherein YN and said amidine or guanidine group are separated by 1 to 6 atoms; and

(amidine or guanidine group) is a group of the formula



in which

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

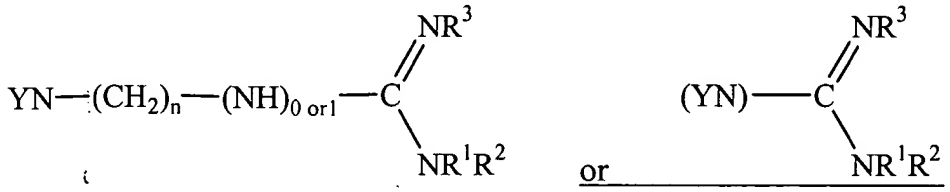
R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms; or

R^1 and R^3 together form an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring including two nitrogen atoms,

or a pharmaceutically acceptable salt thereof,

wherein said compound acts as an analgesic ~~and has reduced or no activity in the central nervous system in comparison to said opioid Y-N~~ that has reduced sedative or addictive effect in comparison to any opioid of formula YN-Q comprising an organic residue YN identical to the organic residue YN of said compound.

7. (Three Times Amended) A compound according to Claim 1, of formula:



~~(II)~~

~~in which YN represents~~ wherein

(YN) is an organic residue obtained by the removal of ~~the R group from an opioid~~ a predetermined organic group, Q, from an opioid of the formula YN-Q, said opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine; ~~of formula (IIIa)~~

~~YN-R~~

~~(IIIa)~~

~~wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,~~

~~Z is NR^3;~~

in which

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms; or

R^1 and R^3 together form an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring including two nitrogen atoms; and

n is an integer of 1 to 6;

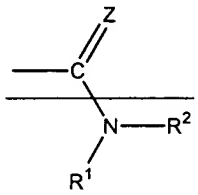
~~and wherein~~

~~R^1 and R^3 may together complete a ring~~

or a pharmaceutically acceptable salt thereof.

8. (Amended) A compound according to Claim 7, in which R^1 and R^3 together form an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring including two nitrogen atoms

~~complete an addition ring, and the grouping~~

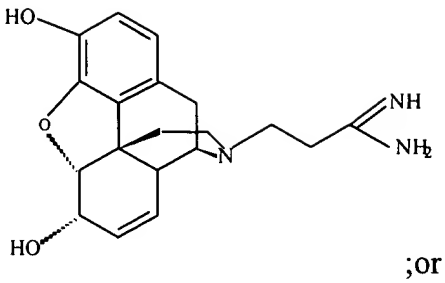


~~forms a heterocyclic moiety~~.

12. (Three Times Amended) A compound according to Claim 7~~8~~, in which R^1 and R^2 are both H.

14. (Three Times Amended) A compound according to Claim 7 ~~12~~, in which the opioid is morphine, codeine or buprenorphine.

16. (Twice Amended) A compound according to Claim 1, ~~in which the compound of formula I is~~ said compound selected from the group consisting of



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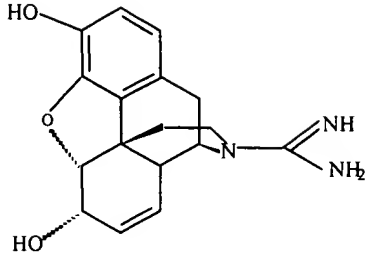

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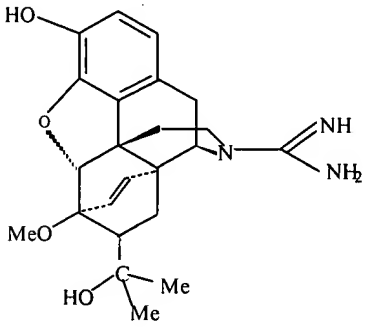

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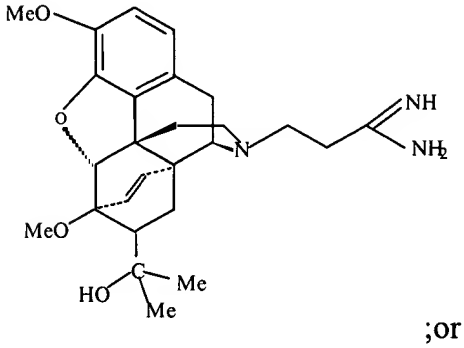

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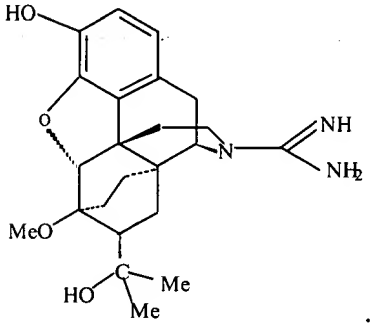

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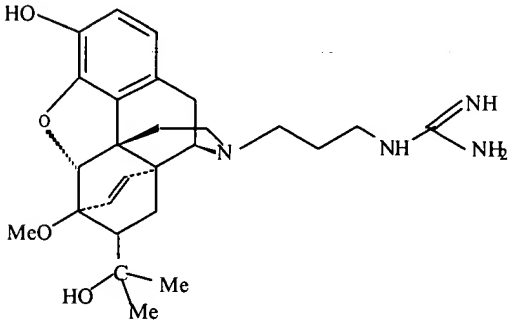

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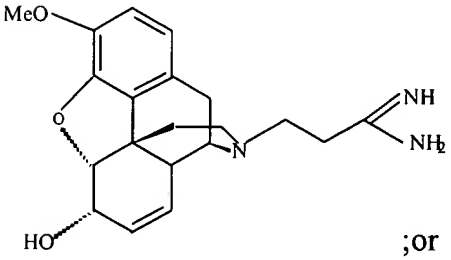

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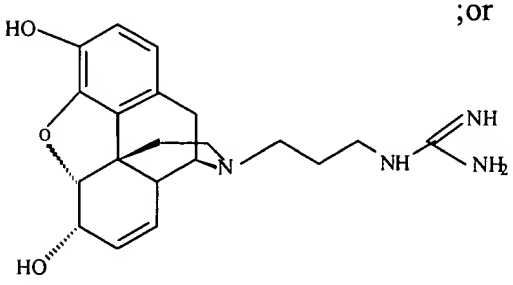

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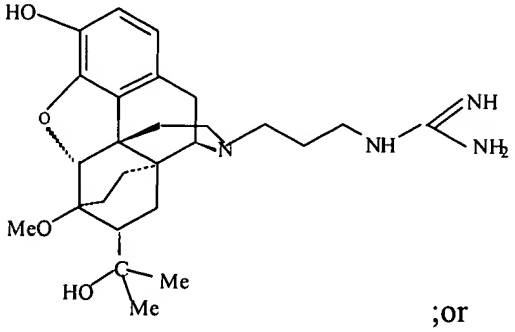

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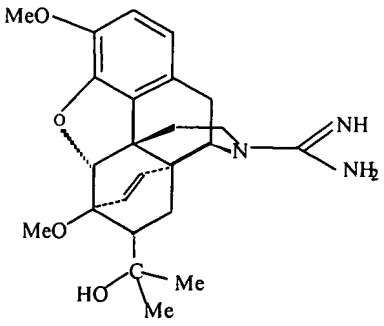


18. Cancelled. ~~(Twice Amended) A method of reducing the central nervous system activity of an opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine, comprising the step of linking the nitrogen atom of said opioid to a spacer group, which in turn is linked to an amidine or guanidine group.~~

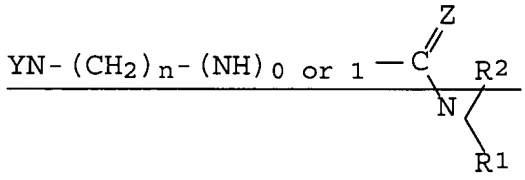
19. (Three Times Amended) A method for the preparation of a compound of ~~formula II~~ claim 7 comprising the step of reacting a compound having the formula

$YN\text{-}(CH_2)_n\text{-}NH_2$

or

YN-H

with a cyanamide of formula R^1NHCN,



~~(II)~~

~~in which~~

~~YN represents an organic residue obtained by removal of the R group from an opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine of formula (IIIa)~~

~~YN-R~~

~~(IIIa)~~

~~wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,~~

~~Z is NR^3;~~

~~R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 atoms;~~

~~R^2 is H or an alkyl group having 1 to 6 carbon atoms;~~

~~R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;~~

~~n is an integer of 1 to 6,~~

~~and wherein~~

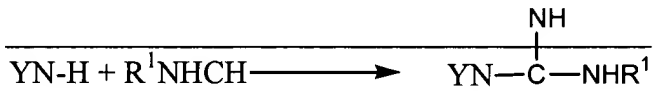
~~R^1 and R^3 may together complete a ring, comprising the steps of~~

~~(a) Reaction of a compound of formula (IV)~~

~~YN-H~~

~~(IV)~~

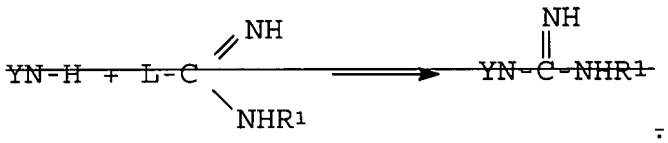
~~with a cyanamide, R^1NHCN, according to the equation~~



~~or~~

~~(b) Reaction of a compound of formula (IV) with a compound of formula (V)~~

~~wherein L is a leaving group, according to the equation~~



wherein

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms; and

n is an integer of 1 to 6.

20. (Three Times Amended) A method for the preparation of a compound of claim 7 comprising the steps of reacting a compound of formula

$$YN\text{-}(CH_2)_n\text{-}(NH)_{0\text{ or }1}\text{-}CN$$

or

$$YN\text{-}CN$$

with H_2S to obtain an N-thiocarboxamide , and then either (i) reacting the N-thiocarboxamide with an amine R^1R^2NH, or

(ii) Methylating the N-thiocarboxamide to yield an isothiourea compound, which is in turn reacted with an amine R^1R^2NH,

wherein

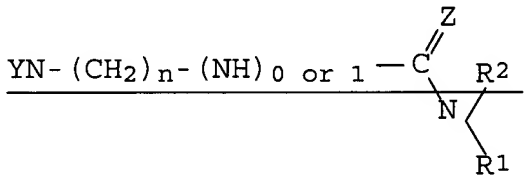
R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H; and

n is an integer of 1 to 6.

~~A method for the preparation of a compound of formula II~~



~~(II)~~

~~in which~~

~~YN represents an organic residue obtained by removal of the R group from an opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine of formula (IIIa)~~

~~YN-R~~

~~(IIIa)~~

~~wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl, Z is O, S or NR^3;~~

~~R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;~~

~~R^2 is H or an alkyl group having 1 to 6 carbon atoms;~~

~~R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;~~

~~n is an integer of 1 to 6,~~

~~and wherein~~

~~R^1 and R^3 may together complete a an addition ring,~~

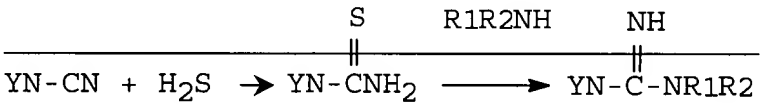
~~comprising the steps of~~

~~(a) Reaction of a compound of formula (VI)~~

~~YN-CN~~

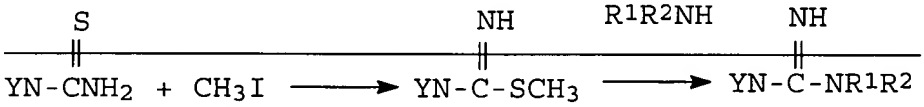
~~(VI)~~

~~with H_2S to obtain an N-thiocarboxamide YN-$CSNH_2$, and optionally (i) reacting the YN-$CSNH_2$ with an amine R^1R^2NH according to the first stage or optionally the two stages of the equation~~



~~to yield a compound of formula II where Z is S if the optional step is not taken, or a compound of formula II where Z is NH if the optional step is taken, or~~

~~(b) (ii) Methylating the N-thiocarboxamide to yield an isothiourea compound, which is in turn reacted with an amine R^1R^2NH:~~



21. (Three Times Amended) A method for the preparation of a compound of claim 7 comprising the step of reacting a compound of formula

YN-$(CH_2)_n$-(NH)-CN

or

with methanol under acidic conditions to yield an isourea, which in turn is reacted with an amine of the formula R^1R^2NH,

wherein

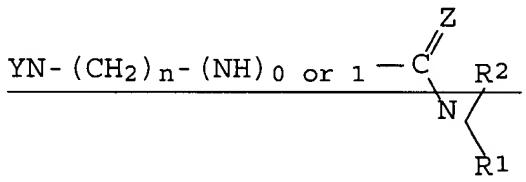
R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H; and

n is an integer of 1 to 6.

~~A method of synthesis of a compounds of formula (II)~~



~~(II)~~

~~in which~~

~~YN represents an organic residue obtained by removal of the R group from an opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine of formula (IIIa)~~

~~YN-R~~

~~(IIIa)~~

~~wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,~~

~~Z is O, S or NR^3;~~

~~R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;~~

~~R^2 is H or an alkyl group having 1 to 6 carbon atoms;~~

~~R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;~~

~~n is an integer of 1 to 6,~~

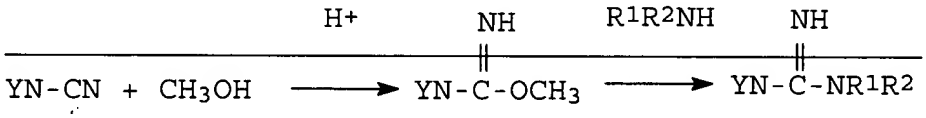
~~and wherein~~

~~R^1 and R^3 may together complete an addition ring, comprising the step of reacting an N-cyano compound of formula (VI)~~

~~YN-CN~~

~~(VI)~~

~~with methanol under acidic conditions to yield an isourea, which in turn is reacted with an amine according to the equation~~



22. (Three Times Amended) A method for the preparation of a compound of claim 7 comprising the step of reacting a compound of formula

$YN-(CH_2)_n-(NH)-CN$

or

YN-CN

with a metallated residue containing - NR^1R^2,

wherein

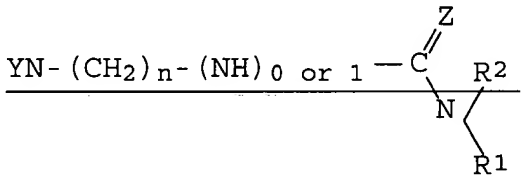
R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H; and

n is an integer of 1 to 6.

~~A method of synthesis of a compound of formula (II)~~



~~(II)~~

~~in which~~

~~YN represents an organic residue obtained by removal of the R group from an opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine of formula (IIIa)~~

~~YN-R~~

~~(IIIa)~~

~~wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,~~

~~Z is NH;~~

~~R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;~~

~~R^2 is H or an alkyl group having 1 to 6 carbon atoms;~~

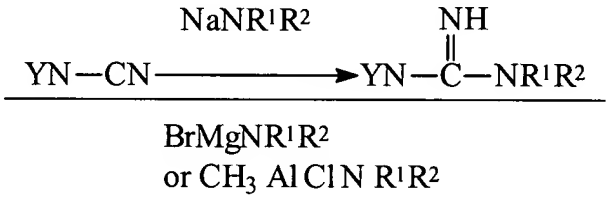
~~n is an integer of 1 to 6,~~

~~and wherein~~

~~R^1 and R^3 may together complete an addition ring, comprising the step of reacting an N-cyano compound of formula (VI)~~

~~YN-CN~~

~~and a metallated residue~~



32. Cancelled. ~~(New) A method of inducing analgesia in a mammal, said method comprising administration of a compound of claim 1 in amounts effective to induce said analgesia.~~

33. (Amended) A method of inducing analgesia in a mammal, said method comprising administration of a pharmaceutical composition of claim 23 in amounts effective to induce said analgesia to a mammal in need thereof.

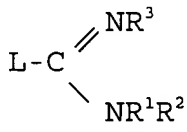
34. (NEW) A method for the preparation of a compound of claim 7 comprising the step of reacting a compound having the formula

$YN\text{-}(CH_2)_n\text{-}NH_2$

or

YN-H

with a compound of formula (V)



(V)

wherein

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

R^1 and R^3 may together be an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring between the two nitrogen atoms, and

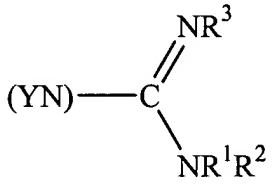
L is a leaving group.

Pending Claims in clean form (GH claims)

1. (Three Times Amended) A compound having the formula:

(YN)-(spacer)-(amidine or guanidine group)

or

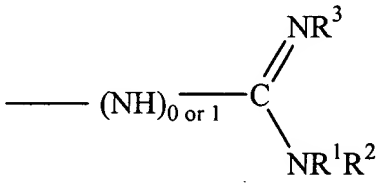


wherein

(YN) is an organic residue obtained by the removal of a predetermined organic group, Q, from an opioid of the formula YN-Q, said opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine;

(spacer) is a group linking YN to an amidine or guanidine group, wherein YN and said amidine or guanidine group are separated by 1 to 6 atoms; and

(amidine or guanidine group) is a group of the formula



in which

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms; or

R^1 and R^3 together form an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring including two nitrogen atoms,

or a pharmaceutically acceptable salt thereof,
wherein said compound acts as an analgesic that has reduced sedative or addictive effect in comparison to any opioid of formula YN-Q comprising an organic residue YN identical to the organic residue YN of said compound.

2. A compound according to Claim 1, in which the spacer is a straight or branched alkyl, alkenyl or alkynyl chain of 1 to 6 carbon atoms.

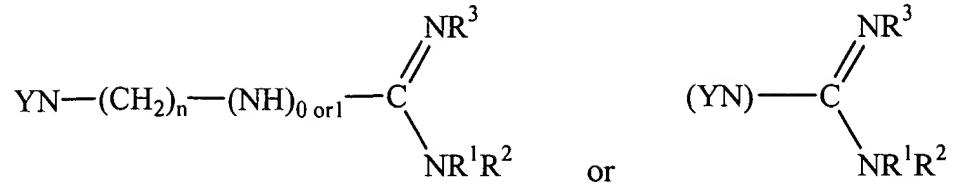
3. A compound according to Claim 1, in which the spacer is a cyclic alkyl, alkenyl or alkynyl group.

4. Cancelled.

5. A compound according to Claim 1, in which the spacer group is of 2 to 3 carbon atoms.

6. Cancelled.

7. (Three Times Amended) A compound according to Claim 1, of formula:



wherein

(YN) is an organic residue obtained by the removal of a predetermined organic group, Q, from an opioid of the formula YN-Q, said opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine;

in which

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms; or

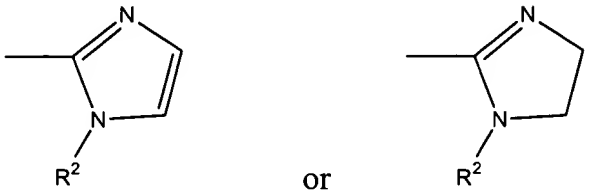
R^1 and R^3 together form an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring including two nitrogen atoms; and

n is an integer of 1 to 6;

or a pharmaceutically acceptable salt thereof.

8. (Amended) A compound according to Claim 7, in which R^1 and R^3 together form an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring including two nitrogen atoms.

9. A compound according to Claim 8, in which the heterocyclic moiety is a 2-imidazolyl or 2-imidazolinyl group of formula:



10. A compound according to Claim 8 or Claim 9, in which R is CH_3.

11. A compound according to Claim 8, in which n is 2 or 3.

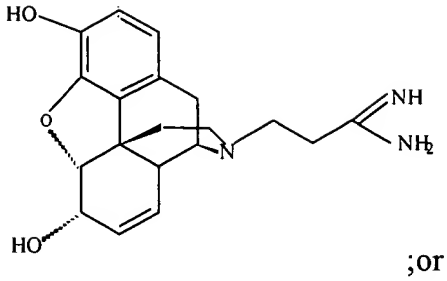
12. (Three Times Amended) A compound according to Claim 7, in which R^1 and R^2 are both H.

13. Cancelled.

14. (Three Times Amended) A compound according to Claim 7 , in which the opioid is morphine, codeine or buprenorphine.

15. Cancelled.

16. (Twice Amended) A compound according to Claim 1, said compound selected from the group consisting of



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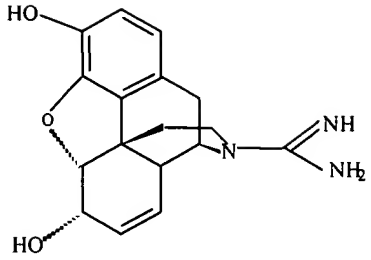

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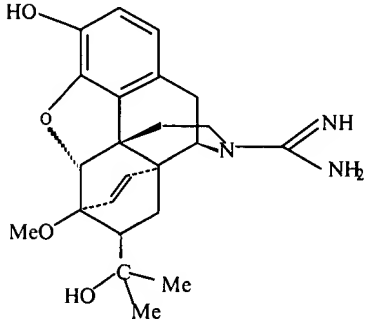

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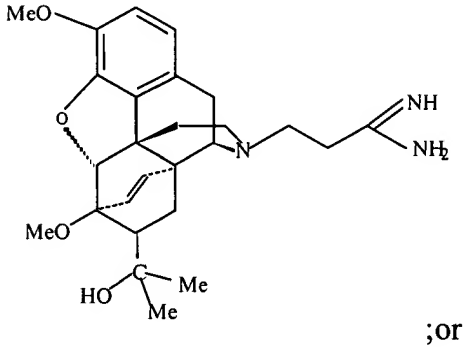

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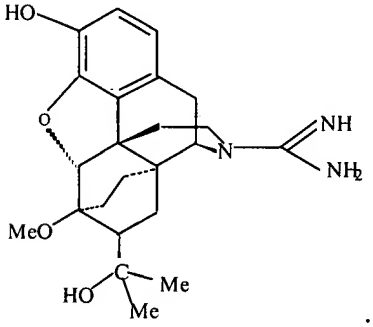

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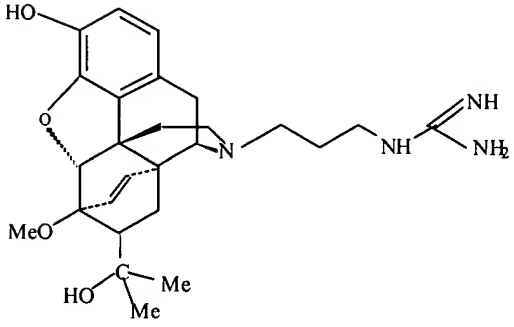

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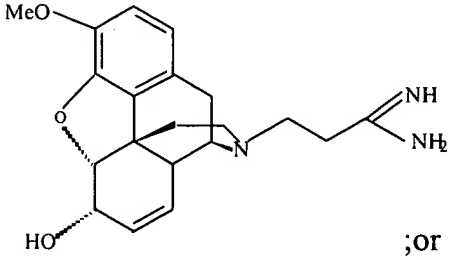

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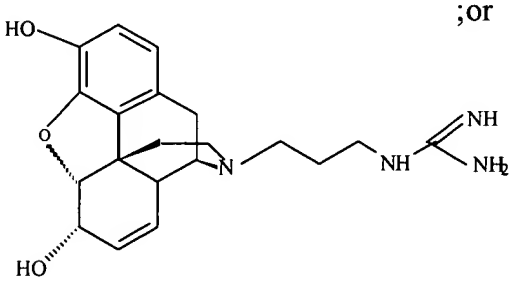

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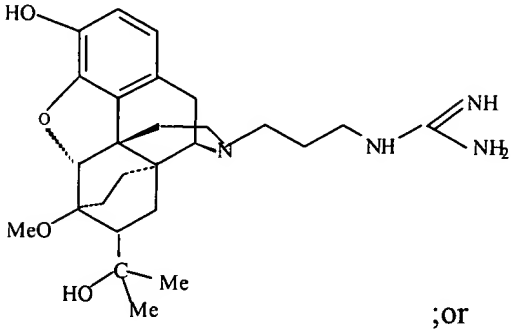

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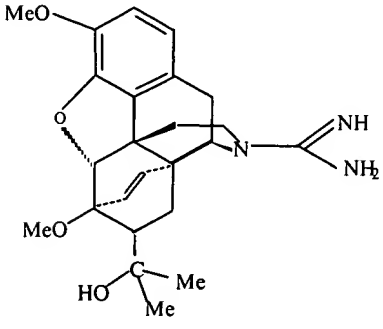


17. Cancelled.

18. Cancelled.

19. (Three Times Amended) A method for the preparation of a compound of claim 7 comprising the step of reacting a compound having the formula

$$YN\text{-}(CH_2)_n\text{-}NH_2$$

or

YN-H

with a cyanamide of formula R^1NHCN,

wherein

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms; and

n is an integer of 1 to 6.

20. (Three Times Amended) A method for the preparation of a compound of claim 7 comprising the steps of reacting a compound of formula

$$YN\text{-}(CH_2)_n\text{-}(NH)_{0\text{ or }1}\text{-}CN$$

or

YN-CN

with H_2S to obtain an N-thiocarboxamide , and then either

(i) reacting the N-thiocarboxamide with an amine R^1R^2NH, or

(ii) Methylating the N-thiocarboxamide to yield an isothiourea compound, which is in turn reacted with an amine R^1R^2NH,

wherein

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H; and

n is an integer of 1 to 6.

21. (Three Times Amended) A method for the preparation of a compound of claim 7 comprising the step of reacting a compound of formula

$$YN\text{-}(CH_2)_n\text{-}(NH)\text{-}CN$$

or

$$YN\text{-}CN$$

with methanol under acidic conditions to yield an isourea, which in turn is reacted with an amine of the formula R^1R^2NH,

wherein

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H; and

n is an integer of 1 to 6.

22. (Three Times Amended) A method for the preparation of a compound of claim 7 comprising the step of reacting a compound of formula

$$YN\text{-}(CH_2)_n\text{-}(NH)\text{-}CN$$

or

with a metallated residue containing - NR^1R^2,

wherein

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H; and

n is an integer of 1 to 6.

23. A composition comprising a compound according to Claim 1, together with a pharmaceutically acceptable carrier.

24. A method of inducing analgesia, comprising the step of administering an effective amount of a compound according to Claim 1 to a mammal in need of such treatment.

25. A method according to claim 24, in which the mammal is a human.

26. Cancelled.

27. Cancelled.

28. A method of inducing analgesia, comprising the step of administering an effective amount of a compound according to claim 7 to a mammal in need of such treatment.

29. A method according to claim 28, in which the mammal is a human.

30. Cancelled.

31. A composition comprising a compound according to Claim 7, together with a pharmaceutically acceptable carrier.

32. Cancelled.

33. (Amended) A method of inducing analgesia in a mammal, said method comprising administration of a pharmaceutical composition of claim 23 in amounts effective to induce said analgesia to a mammal in need thereof.

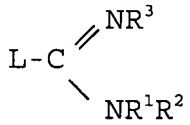
34. (NEW) A method for the preparation of a compound of claim 7 comprising the step of reacting a compound having the formula

$$YN\text{-}(CH_2)_n\text{-}NH_2$$

or

$$YN\text{-}H$$

with a compound of formula (V)



(V)

wherein

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

R^1 and R^3 may together be an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring between the two nitrogen atoms, and

L is a leaving group.